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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,950	12/14/2001	Akira Nakamura	31671-176197	7278

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,950	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 December 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/14/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-7 and 9-11, in the election received on 04/01/2004 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a homozygous disruption in the FcγRIIB gene wherein said mouse has been immunized with type IV collagen and said mouse exhibits alveolar hemorrhage, degeneration of glomus and proximal renal tubule or increased levels of kidney glomerular basement membrane antibody and methods of using said mouse to screen for therapeutics agents for the treatment of the exhibited phenotypes wherein a test substance is administered to said mouse after the disruption is induced, does not reasonably provide enablement for any other non-human animal or methods encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims are drawn to a non-human animal model of Goodpasture's syndrome wherein the animal is deficient for the FcγRIIB gene product as a result of FcγRIIB gene disruption and said animal has been immunized with type IV collagen. Claims are further drawn to methods of using said mouse to screen for agents in the treatment of Goodpasture's syndrome.

The specification teaches generating a knockout of the FcγRIIB gene in mice by targeted insertional mutagenesis in mouse ES cells (page 9, paragraph 3-page 10, paragraph 1). The ES cells were used to make transgenic mice whose genome comprises a disruption of the FcγRIIB gene. The mice were then immunized at 8 weeks of age with type IV collagen (page 10, paragraph 2-3). The combination of the genetic deficiency and immunization resulted in considerably higher levels of antibodies to type IV collagen in comparison to control mice (page 12, paragraph 2). The mice exhibited, as a result, alveolar hemorrhage and degeneration of the glomus and proximal renal tubule (page 11, paragraph 1) and increased levels of kidney glomerular basement membrane antibody (page 12, paragraph 2).

The breadth of the claims is such that they encompass any non-human animal species wherein the animal. The claims also broadly encompass both homozygous and heterozygous animals. The claims fail to recite a specific phenotype for the claimed non-human animal and therefore also encompass any phenotype, including a wildtype phenotype. Claim 4 is so broad as to encompass any model of Goodpasture's syndrome, derived through any means.

1) The specification fails to enable any non-mouse species of non-human animal comprising a targeted gene disruption. The specification teaches targeting the FcγRIIB gene in totipotent mouse embryonic stem cells and using the ES cells to generate transgenic mice (page 9, paragraph 3-page 10, paragraph 1). The specification does not teach any other totipotent ES

cells that are capable of giving rise to all cell types of a non-mouse species. The art at the time of filing held that targeted gene insertion technology was not available for any species other than mouse. Since homologous recombination is required for gene targeting methods, cells in culture must be used for the gene-targeting event. The only cells in culture known to give rise to the germ-line, and are therefore capable of generating a transgenic animal whose genome comprises a targeted gene disruption, are mouse ES cells. Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65). Lederman also highlights the fact that germ-line competent ES cell lines from species other than mouse have not been isolate (2000, Experimental Physiology, Vol. 85, pages 603-613, specifically, page 604, column 1, lines 7-8). Due to the lack of guidance given in the instant specification with respect to totipotent ES cells in non-mouse species, it would require undue experimentation for the skilled artisan to determine how to generate an animal with a targeted gene disruption other than mouse.

2) The specification further fails to enable the claimed non-human animals exhibiting any phenotype, including wild-type. The specification has taught that transgenic mice whose genomes comprise a homozygous disruption of the FcγRIIB gene exhibit alveolar hemorrhage and degeneration of the glomus and proximal renal tubule (page 11, paragraph 1). The specification has failed to teach any other phenotypes for the homozygous mice as encompassed by the claims. The specification has failed, also, to disclose a phenotype for the claimed heterozygous mutant mice.

The art at the time of filing held that the phenotype of transgenic knockout mice was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph).

The claims to the homozygous mice encompass any phenotype. However, the specification teaches only that the mice exhibit alveolar hemorrhage and degeneration of the glomus and proximal renal tubule. As set forth above, the art at the time of filing held that the phenotype of transgenics was unpredictable. Therefore, one of skill in the art would not know how to disrupt a particular gene and predictably arrive at a mouse with any particular phenotype. In the instant case, the skilled artisan would not know how to disrupt the FcγRIIB gene in such a way to cause any phenotype encompassed by the claims other than alveolar hemorrhage, degeneration of the glomus and proximal renal tubule and increased levels of kidney glomerular basement membrane antibody. Accordingly, it would require the skilled artisan undue experimentation to determine how to disrupt a target gene in a mouse in such a way as to generate a mouse exhibiting any phenotype other than alveolar hemorrhage and degeneration of the glomus and proximal renal tubule and increased levels of kidney glomerular basement membrane antibody.

The claims do not recite a phenotype that differs from that of a wild-type mouse. Therefore the claims encompassing the heterozygous mice are interpreted to encompass mice without a phenotype that differs from wildtype. The specification teaches generating a knockout mouse comprising a disruption of the FcγRIIB gene, however, the specification does not teach a phenotype for the heterozygous mouse. One of skill in the art would not know how to use a transgenic knockout mouse that lacks a phenotype because the specification has not provided any guidance correlating to using mice lacking a phenotype. The specification teaches that the claimed mice can be used to screen for remedies for Goodpasture's disease, however, without a disclosure of the phenotype associated with Goodpasture's disease for the heterozygous mice, the skilled artisan would not know what to phenotypes to screen.

3) The breadth of claims 1-7 and 9-11 is such that they encompass chimeric mice (genetic mosaics) wherein only a portion of the cells of the mouse comprises the claimed genetic disruption. The specification fails to enable making chimeric mice such that they exhibit any phenotype other than alveolar hemorrhage and degeneration of the glomus and proximal renal tubule and increased levels of kidney glomerular basement membrane antibody as encompassed by the claims, including a wild-type phenotype.

The specification teaches generating non-chimeric transgenic mice by using chimeric mice and mating them to C57BL/6 mice to generate non-chimeric transgenic mice (see paragraph bridging pages 9-10). The specification teaches that the non-chimeric transgenic mice whose genome comprises a homozygous disruption in the FcγRIIB gene and have been immunized with type IV collagen exhibit degeneration of the glomus and proximal renal tubule and increased levels of kidney glomerular basement membrane antibody. The specification does

not correlate a phenotype to chimeric mice comprising one or more cells with a disruption in the FcγRIIB gene to any phenotype.

The method of making genetic mosaic mice is such that each resulting chimera is comprised of a different, unpredictable ratio of cells of various genotypes. This ratio cannot be predetermined. Furthermore, the spatial distribution of cells of each genotype cannot be predetermined. Therefore, the phenotype of chimeric animals is not only dependent upon the genotype of the cells (which is unpredictable as set forth by the state of the art outlined above, for example see Leonard; Griffiths) but is also dependent upon the spatial distribution of the cells and their relative population size. Thus, the phenotype of the chimeric animals encompassed by the claims is highly unpredictable. The specification fails to provide the guidance necessary to overcome this high level of unpredictability to generate a chimeric mouse exhibiting any specific phenotype or any phenotype other than wildtype. The specification discloses using the claimed mice for screening for agents that affect the phenotype of the claimed mice. As set forth above, without a predictable phenotype, it would require additional and undue experimentation for one of skill in the art to determine a useful phenotype for the claimed chimeric mice and to determine what to screen for. Therefore, without undue experimentation, the skilled artisan would not know how to use the chimeric mice encompassed by the claims.

4) Claims 3 and 5-7 encompass a method of screening for a remedy wherein the non-human animal is made genetically deficient for FcγRIIB after the animal is immunized with type IV collagen. The specification teaches making a knockout mouse by genetically modifying ES cells. The specification does not teach immunizing the claimed animal before making the genetic modification. The specification does not teach how to make the claimed genetic modification in

a non-human animal after immunization in such a way as to lead to a model of Goodpasture's syndrome. It would require undue experimentation for one of skill in the art to determine how to immunize an animal before making a genetic modification in ES cells from which the animal will be derived.

5) Claims 4 and 9-11 encompass any non-human model animal of Goodpasture's syndrome. The specification teaches a mouse model of Goodpasture's syndrome wherein a transgenic mouse whose genome comprises a disruption of the FcγRIIB gene is immunized with type IV collagen wherein the mouse exhibits alveolar hemorrhage, glomerulonephritis or an increase antibody titer to type IV collagen. The specification does not teach any other model of Goodpasture's syndrome. It would require undue experimentation to determine how to make a non-human animal model of Goodpasture's syndrome other than that set forth by the specification.

In view of the state of the art with respect to the unpredictability of phenotype of knockout mice, the underdeveloped art of ES cells at the time of filing and the breadth of the claims with respect to the genus of non-human animal species and the breadth of the phenotype of the claimed animals, there is insufficient guidance in the specification to make and use the claimed non-human animals. Thus, for the reasons given above, it would require undue experimentation for one of skill in the art at the time of filing to implement the invention as claimed with a reasonable degree of success.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear because it states "whose function of immunoglobulin FCγ receptor IIB gene is deficient on its chromosome". This phrase is unclear because the function of a gene cannot be deficient on a chromosome. An animal may be deficient for the function of a gene product due to genetic disruption on a chromosome. Claim 2 depends from claim 1.

Claim 1 is unclear because it does not state what is immunized with type IV collagen. It does not clearly set forth that the non-human animal is immunized. Claim 2 depends from claim 1.

Claim 3 and 4 are incomplete as written. The preamble of the claim is directed to a method for screening for a remedy for Goodpasture's syndrome. However, the claim is incomplete because the method steps do not relate back to the preamble in a positive process. Appropriate correction is required. Claims 5-7 depend from claim 3. Claims 9-11 depend from claim 4.

Claim 4 recites the limitation "the non-human model animal of Goodpasture's syndrome" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

The phrase "appearance of antikidney glomerular basement membrane" renders claims 6 and 10 unclear. It is not clear what "antikidney glomerular basement membrane" is. It is not clear if the phrase is referring to an antibody, having omitted the word "antibody" from the phrase or if the phrase is referring to something else. Appropriate clarification is required.

Claims 6 and 10 are unclear because they recite the phrase "found in the expression of Goodpasture's syndrome". Genes are expressed. Diseases and phenotypes are exhibited, not expressed. Appropriate clarification is required.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

Deborah Crouch

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